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Original Article

## CT Assessment of Subtypes of Pulmonary Emphysema in Females

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We performed a retrospective study examining the prevalence and subtypes of pulmonary emphysema (PE) identified by computed tomography (CT) in females. We reviewed the records of 1,687 female subjects who had undergone CT. They were divided into the following 2 age groups: group A (<50 years) and group B (≥50 years). PE was diagnosed by the presence of low-attenuation areas using visual assessment (grades 0–3) on CT images. Two subtypes of PE were observed: centrilobular emphysema (CLE) and paraseptal emphysema (PSE). PE was divided into the following 3 categories: I (CLE or CLE-predominant); II (CLE and PSE of equal extent); and III (PSE or PSE-predominant). PE was found in 64 of 274 smokers (23.3%) and 54 of 1,413 non-smokers (3.8%). In smoking subjects, when grades 1 and 2 were grouped together as mild PE, the mean age for CT grade 3 (severe PE) was significantly higher than that for mild PE. In group A, category III predominated, whereas category I was more prevalent in group B, in both smoking and non-smoking subjects. A high incidence of PE was found in smoking subjects as compared with non-smoking subjects. PSE predominated in younger subjects, whereas CLE predominated in older subjects.

**Key words:** cigarette smoking, CT, pulmonary emphysema, females

**P**ulmonary emphysema (PE) is defined by the American Thoracic Society as an abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls, most often caused by chronic obstructive pulmonary disease (COPD) or alpha1-antitrypsin deficiency [1, 2]. PE is one of the most important diseases related to cigarette smoking, and smoking causes a large proportion of cases of PE. Computed tomography (CT) is currently the method of choice for

noninvasive assessment of pathologic changes of the alveoli in emphysema, and a high correlation with histopathology has been shown [3, 4].

Based on an epidemiologic study, Fukuchi *et al.* reported that in Japan the prevalence of COPD in the population of smokers older than 40 years was 10.9% overall (men: 16.4%; women: 5.0%) [5]. In addition, it has been reported using CT that PE is observed in more than half of male Japanese smokers [6]. Whether or not females are more susceptible to cigarette smoke than males is controversial [7, 8]. The purpose of the present study was to assess the prevalence and subtypes of PE identified by CT imaging in females.

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## Subjects and Methods

**Subjects.** We reviewed the records of 1,687 female subjects (ranging in age from 25 to 94 years) who had undergone CT scanning at our University Hospital between March 2002 and December 2006 because of suspected lung disease seen on chest radiographs or because of respiratory complaints. Of the 1,687 subjects, 274 were smokers (16.2%) and 1,413 were non-smokers (83.8%). Ex-smokers were included with smokers. The level of serum alpha 1-antitrypsin was not checked because its deficiency is very rare in Japan. Subjects were divided into the following 2 age groups: group A (<50 years); and group B ( $\geq$ 50 years). Institutional review board exemption was obtained, and informed consent was not required.

**CT examination.** Two CT machines (Aquilion; Toshiba; Tokyo, Japan [used at 120 kV and 300 mA] and HiSpeed Advantage RP; Yokogawa; Tokyo, Japan [used at 120 kV and 240 mA]) were used. In all cases, contiguous 1-cm sections encompassed the entire thorax. Hard-copy images were photographed at a 1600-Hounsfield unit (HU) window width and a -800-HU window level (Aquilion, Toshiba) and at a 1,500-HU window width and a -700-HU window level (HiSpeed Advantage RP).

**CT image analysis.** PE was diagnosed on the basis of the presence of low-attenuation areas (LAAs) on CT images using visual assessment. The CT images were evaluated independently by 2 experienced radiologists who did not have information as to whether the subject was from the group of smokers or non-smokers. Any difference of opinion was resolved by consensus.

According to the extent of LAAs in the peripheral lung fields, the CT findings were classified into the

following four grades: grade 0 (no LAAs); grade 1 (sparse, scattered small LAAs up to 5 mm in diameter); grade 2 (adjacent LAAs up to 10 mm in diameter); and grade 3 (LAAs > 10 mm that were adjacent to or indistinguishable from each other) [9].

PE is usually classified into the following 3 main subtypes: centrilobular emphysema (CLE); panlobular emphysema (PLE); and paraseptal emphysema (PSE) [10]. In the present study, there were no subjects with PLE. Therefore, PE was classified into the following 3 categories based on the presence of CLE and PSE: I (CLE or CLE-predominant); II (CLE and PSE of equal extent); and III (PSE or PSE-predominant).

**Statistics.** Differences between groups were analyzed by Student's *t* test or the chi-square test. Significance was determined at the  $p < 0.05$  level.

## Results

Table 1 shows the prevalence of PE detected by CT. Of the total of 1,687 female subjects, PE was present in 118 (7.0%). PE was found in 64 of 274 smokers (23.3%) and 54 of 1,413 non-smokers (3.8%). In non-smokers with PE, none had a previous diagnosis of collagen diseases. The prevalence of PE was significantly higher in smokers than non-smokers ( $p < 0.0001$ ). There was no significant difference between mean ( $\pm$ SD) age in smoking ( $63.5 \pm 15.2$ ) and non-smoking ( $65.2 \pm 14.3$ ) subjects with PE. The percentage of subjects with PE increased with age.

There were no significant differences between CT grade and mean ( $\pm$ SD) age in smoking and non-smoking subjects (Table 2). However, when grades 1 and 2 in smokers were grouped together as mild PE, the mean ( $\pm$ SD) age for CT grade 3 (severe PE) ( $69.1 \pm$

**Table 1** Prevalence of PE detected by CT in 1,687 female subjects according to age group

Age group	Smoking status	Subjects with PE/total	%
Group A (< 50 years)	Smoker	11/61	18.0
	Non-smoker	7/230	3.0
Group B ( $\geq$ 50 years)	Smoker	53/213	24.9
	Non-smoker	47/1,183	4.0
All subjects	Smoker	64/274	23.3
	Non-smoker	54/1,413	3.8
Total		118/1,687	7.0

PE, pulmonary emphysema.

9.4) was significantly higher than that for mild PE ( $61.2 \pm 16.2$ ) ( $p < 0.05$ ). In smokers, there were no statistically significant differences in smoking indices according to CT grade within each age group (Table 3). In 64 smoking subjects with PE, although there was also no statistically significant difference in smoking indices between group A ( $16.4 \pm 3.4$ ) and group B ( $33.9 \pm 4.5$ ) ( $p = 0.08$ ), the smoking indices of group B tended to be higher than those of group A.

In group A, category III predominated (Fig. 1), whereas category I was more prevalent in group B (Fig. 2), in both smoking and non-smoking subjects (Table 4). There was a statistically significant difference between subjects in groups A and B ( $p < 0.05$ ) among both smokers and non-smokers especially with

respect to the prevalence of subjects in categories I and II combined and the prevalence of subjects in category III in each age group.

## Discussion

In the present study comprising 1,687 female subjects, a high incidence of PE was found in smoking subjects (23.3%) as compared with non-smoking subjects (3.8%). Smoking in female subjects may be an important cause of PE. The percentage of subjects with PE increased with age. Furthermore, the mean age of the severe PE group was significantly higher than that of the mild PE group. The prevalence of CLE was greater in older females.

**Table 2** CT grades of PE and age in 64 smoker and 54 non-smoker subjects with PE

Smoking Status		CT Grade		
		1	2	3
Smokers	n	30	17	17
	Age, mean $\pm$ SD (years)	$57.4 \pm 18.6$	$66.1 \pm 16.3$	$69.1 \pm 9.4$
Non-smokers	n	33	12	9
	Age, mean $\pm$ SD (years)	$67.8 \pm 14.2$	$60.9 \pm 14.8$	$61.6 \pm 10.8$

PE, pulmonary emphysema.

**Table 3** CT grades of PE and smoking indices in 64 smoker subjects with PE

Smokers		CT Grade		
		1	2	3
Group A	n	8	3	0
	Smoking, mean $\pm$ SD, Pack-years	$16.7 \pm 11.7$	$15.7 \pm 8.2$	
Group B	n	22	14	17
	Smoking, mean $\pm$ SD, Pack-years	$30.2 \pm 28.1$	$29.6 \pm 33.4$	$43.9 \pm 33.2$

PE, pulmonary emphysema. One pack-year: 1 package of cigarettes (20 cigarettes) daily for one year.

**Table 4** Category subtypes of PE in 64 smoker and 54 non-smoker subjects with PE

Smoking Status			Category Subtype		
			I	II	III
Smokers	Group A	n (%)	4 (36.4)	0	7 (63.6)
	Group B	n (%)	36 (67.9)	4 (7.5)	13 (24.5)
Non-smokers	Group A	n (%)	2 (28.6)	0	5 (71.4)
	Group B	n (%)	29 (61.7)	3 (6.4)	15 (31.9)

PE, pulmonary emphysema.

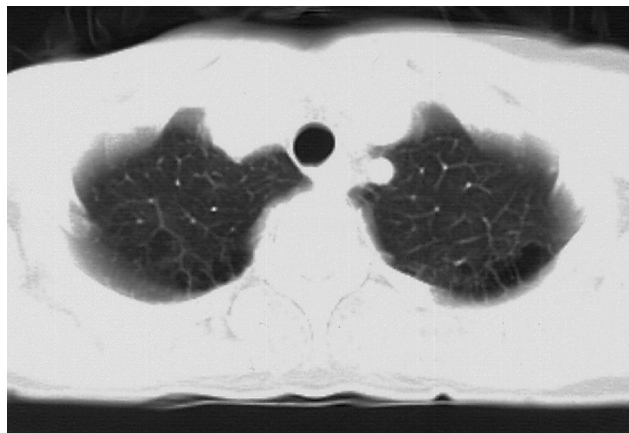


Fig. 1 CT image of a subject with grade 2, category III PE in age group A (a 46-year-old female non-smoker). LAAs adjacent to the chest wall are seen.

LAAs=low-attenuation areas

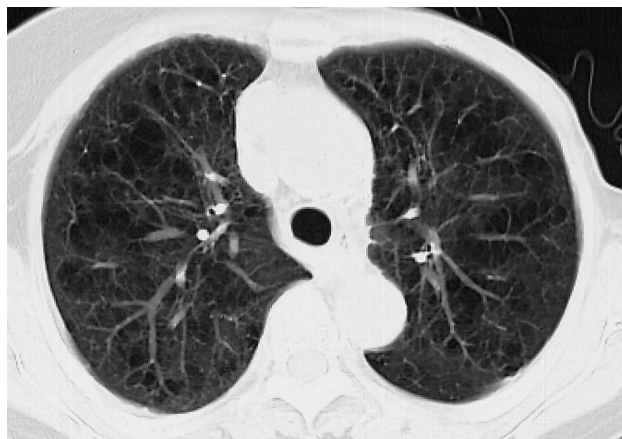


Fig. 2 CT image of a subject with grade 3, category I PE in age group B (a 68-year-old female, with cigarette consumption of 40 pack-years). LAAs > 10mm in diameter fuse with each other in the whole of the upper and middle lung fields.

LAAs=low-attenuation areas

Omori *et al.* have reported that among Japanese male subjects undergoing annual health care examinations the prevalence of PE was 30.5% in current smokers and 3.0% in non-smokers [11]. Camiciottoli *et al.* reported that the prevalence of PE was 30.3% in male smokers and 19.8% in female smokers [12]. Autopsy studies have reported an increase in the incidence of PE with age [13]. Hatayama *et al.* reported that the mean age of the mild PE group was higher than that in the subtle PE group [14]. These findings are consistent with the present study.

In the present study, we found no correlation between the number of packs of cigarettes smoked per year (packs/year) and the severity of PE. This appears to be counterintuitive, because cigarette consumption is clearly a major risk factor for the development of PE, as the severity of PE increases with the number of cigarettes smoked [15,16]. However, similar results have also been previously reported [17]. Although Wang *et al.* found a distinct correlation between smoking and the prevalence of PE, indexes of smoke exposure did not correlate with the extent of CT abnormalities [18]. Gillooly and Lamb also reported no correlation between smoking habits and the extent of microscopic emphysema [19].

Chen *et al.* showed that cigarette consumption may be more detrimental in its effects on lung function in women than in men [20]. Langhammer *et al.*, in a survey of more than 65,000 men and women in

Norway, noted that, of current and previous smokers, women were significantly more likely than men to report respiratory symptoms and asthma, even after the authors controlled for packs/year of smoking and current levels of cigarette smoking per day [21]. This study concluded that women seemed to be more susceptible to the effect of tobacco smoking than men [21].

The prevalence of CLE was greater in older females in the present study. This result is similar to that of a previous study in which the prevalence of CLE was reported to rise with age [6]. CLE was reported to be the most common form of PE and has a proven association with cigarette smoking [1,11]. PSE can occur as an isolated phenomenon in young adults [1]. However, category III (PSE or PSE-predominant) PE in the present study was found not only in younger subjects but also in older subjects. Satoh *et al.* reported a high incidence of PSE in younger male smoking subjects [6]. The pathogenesis of emphysema is often explained by the hypothesis of an imbalance between locally acting proteolytic and anti-proteolytic mechanisms within the lungs [22]. Lysosomal enzymes released by neutrophils and macrophages during an inflammatory reaction can damage the lung parenchyma [22]. However, PSE is not well understood. Pleural pressure gradients might be important. There are isolated case reports describing early-onset emphysema in young patients without a

significant smoking history and with a normal alpha-1-antitrypsin level [23, 24]. These reports suggest that other genetic and environmental risk factors may also play role in the development of emphysema. PSE occurs in young adults who are tall and thin. It is characterized as an enlarged airspace at the periphery of the acini [25]. The lesion is usually limited in extent and occurs most commonly along the dorsal surface of the upper lung. PSE patients are asymptomatic, but the condition is considered to be a cause of pneumothorax in young adults [25].

In the present study, a significantly higher prevalence of PE was seen in smokers than non-smokers. Nonetheless, PE was found in 3.8% of non-smokers. A similar rate of occurrence of PE in non-smokers was also reported by Wang [18]. Involuntary exposure to environmental tobacco smoke is also serious and an entirely preventable public hazard. It has become clear that environmental tobacco smoke adversely affects the health of all who breathe in its toxins. Independent of active smoking, environmental tobacco smoke exposure is a modified risk factor for COPD and lung cancer [26, 27]. Simoni and coworkers reported that environmental tobacco smoke exposure is a risk factor for respiratory health in women who have never been smokers [8].

Smoking groups are defined as follows: 'never smokers,' 'ex-smokers,' and 'current smokers.' In the present study, the non-smoking subjects were 'never smokers' according to their medical records. However, the present study did not evaluate whether or not the non-smoking subjects had been exposed to environmental smoke. Further studies that account for passive smoking are required to evaluate the incidence of PE in female subjects.

The present findings suggest that CT detects PE at an early stage. The percentage of subjects with PE increased with age. The provision of a smoking cessation program for young female subjects with PE should be considered an important strategy to help prevent progression of the disease.

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